Syntheses and Characterization of Some 3,4,5-Trimethoxybenzoyl; 3,4,5-Trimethoxybenzyl; and 3,4,5-Trimethoxyphenylethyl Derivatives of Piperazine and Some Related Compounds

By
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Last but not least he wishes to thank his wife, Faye, for the way in which she uncomplainingly and patiently assumed the role of a "lab widow."

PREFACE

This dissertation is divided into six chapters. The first chapter is the introduction which includes reasons for undertaking this research. The second chapter lists the syntheses and sources of intermediates used in this investigation. The third chapter gives the syntheses and physical characteristics of a number of 3,4,5-trimethoxybenzamides. The syntheses and physical characteristics of a number of 3,4,5-trimethoxybenzylamines and their hydrochlorides are described in the fourth chapter. The fifth chapter sets forth the syntheses and physical characteristics of a group of 2-(3,4,5-trimethoxyphenyl)ethyl piperazine hydrochlorides. The sixth chapter summarizes this investigation.

All yields are based on the reactant present in the least stoichiometric quantity.

All temperatures refer to the centigrade scale; its symbol is omitted. Melting points are corrected and were determined with a thermometer calibrated against a Bureau of Standards corrected thermometer.

References are listed in the manner used by journals of the American Chemical Society. Abbreviations of journal names are those used by Chemical Abstracts.

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CHAPTER I

INTRODUCTION

Modern man's life is not only far more comfortable than that of his ancestors'; it is longer and healthier as well. A large part of this achievement has been made possible by therapeutically active synthetic chemicals.

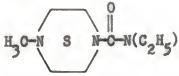
Currently, these drugs are used in almost every field of medicine with varying degrees of success. There is certainly no evidence that we have come close to exhausting the number of potential drugs that have not been clinically evaluated. Many have not been evaluated for the simple reason that they have never been synthesized.

The basic aim of this investigation was to synthesize a number of compounds which would have a reasonable chance of exhibiting some type of desirable pharmacological action. (It should be realized, however, that one cannot predict the pharmacological action of a compound containing any functional group unless one very closely follows the structural pattern of a physiologically active configuration.)

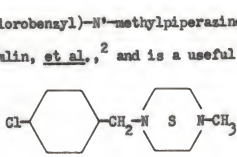
An examination of the structures of the drugs in current use reveals that a great number of them contain nitrogen. This is usually present as an amino or an amido function. The following are a few examples of drugs of these types:

(a) N-Diethylcarbamyl-N'-methylpiperazine (Hetrasan) is useful against the larvae of certain filarial nematodes and was first

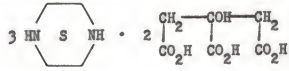
synthesized by Kushner, et al.[1]



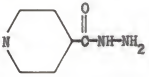
(b) N-(4-Chlorobenzyl)-N'-methylpiperazine (Di-Paraline) was first prepared by Hamlin, et al.,[2] and is a useful antihistaminic drug.



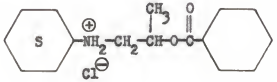
(c) Piperazine citrate (Antepar), prepared by Pollard and Prigot,[3] is a useful vermifuge salt.



(d) Isonicotinic acid hydrazide (Isoniazid) was found by Chorine[4] to have tuberculostatic action.



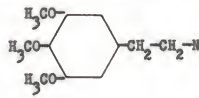
(e) 1-Cyclohexylamino-2-propyl benzoate hydrochloride (Hexylcaine hydrochloride) was found by Kuna and Seeler[5] to be a local anesthetic.



Whereas the number of drugs containing the 3,4,5-trimethoxyphenyl group is not as large as those containing nitrogen, much work is being done in preparing compounds containing this functional group. In particular, Schiemenz and Englehard, at the Organic and Physiological Chemistry Institute at the University of Gottengen[6,7,8] are very active in this area.

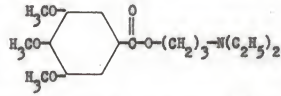
A few examples of the 3,4,5-trimethoxyphenyl compounds that are physiologically active are the following:

(a) 2-(3,4,5-Trimethoxyphenyl)ethyl amine (mescaline).



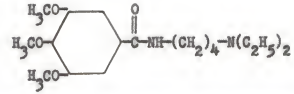
This drug causes unusual psychic effects and visual hallucinations as described by Hoch.[9] (Mescaline occurs in the dumpling cactus found in the Rio Grande Valley and was chewed by the American Indian tribes in that area for religious purposes.)

(b) 3-(N,N-Diethylamino)propyl 3,4,5-trimethoxybenzoate.



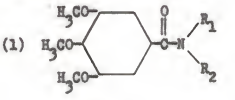
This compound was prepared by Miller and Weinberg.[10] It exhibits a tranquilizing effect.

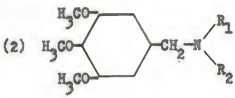
(c) N-[4-(N',N'-Diethylamino)butyl]-3,4,5-trimethoxybenzamide was synthesized by Sastry and Lasslo[11] as a potential sedative.

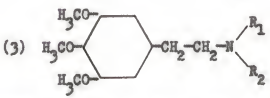


The possibility that the 3,4,5-trimethoxybenzoyl; 3,4,5-trimethoxybenzyl; and 2-(3,4,5-trimethoxyphenyl)ethyl derivatives of N-substituted piperazines and other amino compounds might exhibit some desirable pharmacological activity was the basis for undertaking this investigation.

This dissertation describes the mode of preparation and physical properties of the three series of compounds shown below, as well as proof of their structures where necessary.







All of these compounds are new. They will be submitted to Parke, Davis and Company for pharmacological testing. Reports from these testing programs will be utilized in planning further synthetic studies.

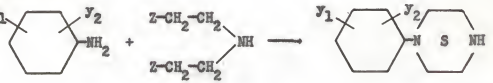
CHAPTER II

INTERMEDIATES

A. General

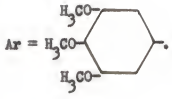
Not many of the intermediate compounds needed in this investigation were available from commercial sources. Thirteen N-substituted piperazines were synthesized. Five were obtained from commercial sources, as were cyclohexylamine and N,N-dimethylhydrazine. The substituents on the N-alkyl piperazines were CH_3-, $HOCH_2CH_2-$ and $3\text{-}CH_3\text{-}C_6H_4\text{-}CH_2-$. The substituents on the phenyl groups of the N-phenyl piperazines were H-, $2\text{-}CH_3-$, $3\text{-}CH_3-$, $4\text{-}CH_3-$, 2-Cl-, 4-Cl-, $2\text{-}CH_3\text{-}3\text{-}Cl-$, $2\text{-}CH_3\text{-}5\text{-}Cl-$, $2\text{-}Cl\text{-}5\text{-}CH_3-$, $3\text{-}Cl\text{-}4\text{-}CH_3-$, $2\text{-}C_2H_5-$, $2\text{-}CH_3O-$, $2\text{-}C_2H_5O-$ and $2,5\text{-}Cl_2-$.

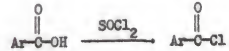
The piperazines were prepared according to the simplified equation below:



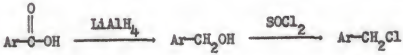
Z = Br or OH

3,4,5-Trimethoxybenzoyl chloride (I); 3,4,5-trimethoxybenzyl chloride (II); and 2-(3,4,5-trimethoxyphenyl)ethyl chloride (III) were prepared as shown in the simplified equations below, where

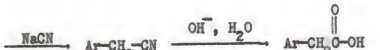


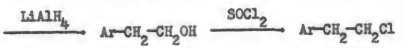


I



II





III

B. Piperazines

The following piperazines were furnished by Carbide and Carbon Chemicals Company, a division of Union Carbide Corporation:

Piperazine

N-Methylpiperazine

N-Phenylpiperazine

N-(2-Hydroxyethyl)piperazine

The Chemo Puro Manufacturing Corporation supplied the N-(2,5-dichlorophenyl)piperazine.

The Benzol Products Company furnished the N-(3-methylbenzyl)-piperazine.

The method of Pollard, et al.,[12,13] was used to prepare the following:

N-(2-Chlorophenyl)piperazine

N-(3-Chlorophenyl)piperazine

N-(4-Chlorophenyl)piperazine

N-(2-Tolyl)piperazine

N-(3-Tolyl)piperazine

N-(4-Tolyl)piperazine

N-(2-Ethylphenyl)piperazine

This consists of heating the arylamine hydrochloride with diethanolamine hydrochloride for eight hours at 240° to produce the dihydrochloride of the N-aryl piperazine. This dihydrochloride is reacted with concentrated sodium hydroxide to liberate the free N-aryl piperazine which is then purified by distillation at reduced pressure.

The method of Prelog, et al.,[14,15] as modified by Parcell[16] was used to synthesize the following:

N-[(2-Methyl-3-chloro)phenyl]piperazine

N-[(2-Methyl-5-chloro)phenyl]piperazine

N-[(2-Chloro-5-methyl)phenyl]piperazine

N-[(3-Chloro-4-methyl)phenyl]piperazine

N-(2-Methoxyphenyl)piperazine

N-(2-Ethoxyphenyl)piperazine

This consists of heating the free arylamine with bis-(2-bromoethyl)amine hydrobromide in chlorobenzene and triethylamine at reflux temperature for eight hours. The chlorobenzene is then removed by steam distillation and the residue neutralized with concentrated sodium hydroxide. The free amine is purified by distillation at reduced pressure.

In the preparation of the N-aryl piperazines, the method of Pollard, et al.,[12,13] was used whenever possible because all the starting materials required by this method are commercially available. Also, this method requires less time and attention than Parcell's[16] method which necessitates the preparation of bis-(2-bromoethyl)amine hydrobromide. The advantages of Parcell's method[16] over the method of Pollard, et al.,[12,13] were higher yields, less cleavage of ether linkages, and better solubilities. In some instances Parcell's method[16] yields homogeneous reaction mixtures, whereas the method of Pollard, et al.,[12,13] does not. The (chloro-methyl) aniline hydrochlorides are not soluble enough to use the method of Pollard, et al.,[12,13] in the preparation of their phenyl piperazine derivatives.

C. Trimethoxyphenyl Compounds

The 3,4,5-trimethoxybenzoic acid was supplied by Kay-Fries Chemicals Incorporated.

The 3,4,5-trimethoxybenzoyl chloride was prepared by reacting thionyl chloride with a solution of 3,4,5-trimethoxybenzoic acid in

chloroform. The reaction mixture was refluxed, under water aspirator vacuum, for one-half hour and then stirred under a very slight vacuum (about 500 mm. Hg) for four hours. The excess thionyl chloride and the chloroform were then removed by heating on a steam bath under water aspirator vacuum. The product was poured into a beaker and allowed to crystallize.

The 3,4,5-trimethoxybenzyl alcohol was synthesized by reacting 3,4,5-trimethoxybenzoic acid with lithium aluminum hydride in a dioxane-ether medium and stirring the mixture for twelve hours. This reaction mixture was subjected to a basic hydrolysis and stirred twelve hours before filtering. The product was obtained by vacuum distillation of the dioxane-ether-water solution.

The 3,4,5-trimethoxybenzyl chloride was prepared by adding thionyl chloride to a solution of 3,4,5-trimethoxybenzyl alcohol in ether while it was cooled in a dry ice bath. The dry ice bath was then removed and the reaction mixture was allowed to warm to room temperature while the reaction flask was kept under water aspirator vacuum. It was allowed to remain under these conditions for eighteen hours. The residue was recrystallized from ether and this product recrystallized from hexane.

The preparation of 3,4,5-trimethoxybenzyl cyanide involved some difficulty. Numerous attempts were made to utilize the method reported by Schiemens and Englehard.[8] This method consists of refluxing 3,4,5-trimethoxybenzyl chloride (0.014 mole), potassium cyanide (0.100 mole), ethanol (50 ml.), and water (12.5 ml.) for three hours. The alcohol is then removed by distillation at 16 mm. Hg

and the residue extracted twice with 30 ml. portions of ether. On evaporation of solvent, Schiemens and Englehard[8] obtained a crude yield of 2.89 g. (99% of the theoretical yield of 3,4,5-trimethoxybenzyl cyanide) which they recrystallized from ligroin.

The author, however, was never able to obtain crystalization of the crude product on the evaporation of the solvent. The best yield he obtained of the crude product was 46%, in spite of carefully following the directions of Schiemens and Englehard[8] as well as trying minor modifications. In all attempts, there was extensive decomposition on heating as indicated by rapid darkening of the solution, loss of starting material, and poor yields of product.

It is believed that these difficulties are the result of the highly polar character of the solvents used, as well as the fact that both water and ethanol can react with the 3,4,5-trimethoxybenzyl chloride. Under these conditions, one would expect a large amount of S_N1 reaction (because of the stability of the 3,4,5-trimethoxybenzyl carbonium ion) which would lower the yield of product.

Therefore, an attempt was made to prepare 3,4,5-trimethoxybenzyl cyanide under S_N2 conditions by refluxing the 3,4,5-trimethoxybenzyl chloride (0.5 mole) with sodium cyanide (1.0 mole) in acetone (3 liters) for one week. The reaction mixture was reduced in volume to 500 ml. by a rotary evaporator and the nitrile hydrolyzed by refluxing it overnight in sodium hydroxide (0.625 mole), methanol (225 ml.) and water (525 ml.). The methanol and the rest of the acetone were then removed on a rotary evaporator. The aqueous solution was acidified with concentrated hydrochloric acid to a pH of about one.

When the sides of the container were scratched, the product, 3,4,5-trimethoxyacetic acid, precipitated. It was recrystallized by dissolving it in chloroform and reprecipitating it with pentane. The overall yield for the two-step syntheses was 75%. This is far superior to the best yield of the two-step syntheses under the S_N1 conditions which was 28%. The 2-(3,4,5-trimethoxyphenyl)ethanol was synthesized from 3,4,5-trimethoxyphenylacetic acid by the procedure described previously for the preparation of 3,4,5-trimethoxybenzyl alcohol.

The 2-(3,4,5-trimethoxyphenyl)ethyl chloride was made from the 2-(3,4,5-trimethoxyphenyl)ethanol by diluting the chloride with pyridine and placing the solution in a flask cooled by an ice bath. To this, thionyl chloride was slowly added while the solution was being stirred. The ice bath was then removed and stirring continued for four hours. The mixture was extracted with ether and the ether extracts washed with water. The pure product was obtained by vacuum distillation of the ether solution.

D. Miscellaneous Compounds

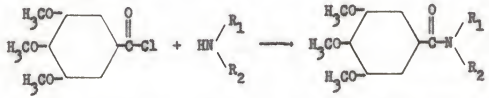
The cyclohexyl amine used was supplied by the Monsanto Chemical Company. The N,N-dimethylhydrazine was obtained from the Olin Mathieson Chemical Corporation.

CHAPTER III

3,4,5-TRIMETHOXYBENZAMIDES

A. General

A group of eighteen amides was prepared by reacting 3,4,5-trimethoxybenzoyl chloride with various amines (N-substituted piperazines in all but one case).



Rather than to discuss in detail the synthesis of each compound, two general procedures will be given. The first method was used to prepare the first twelve compounds and the second method was used for the last six compounds. The basic difference between the two methods is that benzene was used as the reaction medium in the first method whereas chloroform was used in the second method. The second method is the preferred one since it involves a more rapid reaction as well as better solvation of product and by-product. All the compounds could have been made by this procedure.

The author will, therefore, state which general method was used to prepare each individual compound and will discuss any modifications of that method. The molecular formula, molecular weight, melting point, per cent yield and analytical data of each compound are

tabulated in Table I on page 23. The solubility data are recorded in Table II on page 27. The infrared spectra of all the 3,4,5-trimethoxybenzoyl compounds were recorded on a Perkin-Elmer Infracord Spectrophotometer, Model 137B, using sodium chloride cells and prisms and are in the possession of Dr. H. H. Sisler of the University of Florida. Analyses of these spectra confirm the structures of the compounds.

The infrared spectra of these 3,4,5-trimethoxybenzamides show carbonyl absorption in the range 1640-1610 cm.$^{-1}$. This corresponds to the lower frequency limit reported in the literature (1680-1630 cm.$^{-1}$) and actually extends the limit slightly. The appearance of the carbonyl band at these low frequencies can be explained by considering the amount of double band character present in the carbonyl groups of these amides relative to other amides which do not have 3,4,5-trimethoxyphenyl groups conjugated with the carbonyl function.

The fact that the absorption is at a lower frequency than the carbonyl absorption of other amides must be because of the large electron donating effect of the 3,4,5-trimethoxyphenyl group to the carbonyl function. This would enhance the contribution of the polar cannonical form of the molecule and would, therefore, reduce the amount of double bond character present in the carbonyl group. This would account for the absorption of the carbonyl group at lower than normal frequencies.

B. Method 1

3,4,5-Trimethoxybenzoyl chloride (0.04 mole), N-substituted piperazine (0.04 mole), and benzene (100 ml.) are placed in a beaker, stirred briefly and allowed to stand for two hours. The reaction mixture is then washed successively with two 40 ml. portions of 5% sodium hydroxide solution and one 40 ml. portion of water. The benzene is removed on a rotary evaporator. The residue is dissolved in 50 ml. of ethanol and cooled in a dry ice bath. When the walls of the container are scratched, crystallization occurs. The liquids are now removed by filtration and the solid product recrystallized from an ether-ethanol solution.

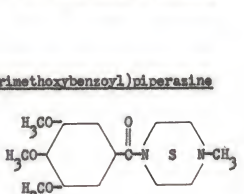
C. Method 2

3,4,5-Trimethoxybenzoyl chloride (0.04 mole), N-substituted piperazine (0.04 mole), and chloroform (100 ml.) are placed in a beaker, stirred briefly, and heated gently on a steam bath for one hour. Enough chloroform is added to dilute the solution to 100 ml. The solution is then washed successively with two 40 ml. portions of 5% sodium hydroxide solution and one 40 ml. portion of water. The chloroform is removed on a rotary evaporator. The residue is dissolved in 50 ml. of ethanol and cooled in a dry ice bath. When the walls

of the container are scratched, crystallization occurs. The liquids are now removed by filtration and the solids product recrystallized from a 50% aqueous ethanol solution.

D. Individual Procedures

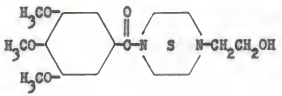
N-Methyl-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 2

(b) Modifications -- On evaporation of the chloroform, the residue was dissolved in 25 ml. of ethanol and 200 ml. of ether. The product was recrystallized from a 10% ethanolic ether solution.

N-(2-Hydroxyethyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine

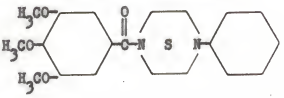


(a) Method 2

(b) Modification -- On evaporation of the chloroform, the liquid residue was allowed to stand under a layer of ether for two hours. A few crystals formed and when they were scratched against

the walls of the container for fifteen minutes the entire residue solidified. These solids were dissolved in a chloroform-ether mixture. On cooling, two layers formed and when the lower one was scratched against the side of the container it solidified. This material was then pulverized and washed with ether.

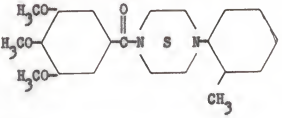
N-Phenyl-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modifications -- 3,4,5-Trimethoxybenzoyl chloride (0.04 mole), N-phenyl piperazine (0.08 mole), and benzene (50 ml.) were placed in a beaker and allowed to stand overnight. The mixture was filtered and the benzene removed on a rotary evaporator. The residue was then dissolved in acetone and Norite A added. The solution was boiled and filtered. The acetone was removed on a rotary evaporator and 150 ml. of benzene was added to the residue. This solution was washed successively with two 30 ml. portions of 5% hydrochloric acid, one 30 ml. portion of water, two 30 ml. portions of 5% sodium hydroxide solution and one 30 ml. portion of water. The rotary evaporator was then used to remove the benzene and the crystalline residue was recrystallized from ether.

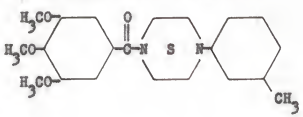
N-(2-Tolyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modifications -- 3,4,5-Trimethoxybenzoyl chloride (0.04 mole), N-(2-tolyl)piperazine (0.08 mole), benzene (50 ml.), and acetone (25 ml.) were placed in a beaker and allowed to stand for one hour. A solid, N-(2-tolyl)piperazine hydrochloride, formed and was removed by filtration. The solvent was removed from the filtrate on a rotary evaporator and the residue dissolved in 150 ml. of benzene. This solution was successively washed with two 30 ml. portions of 5% hydrochloric acid, one 30 ml. portion of 5% sodium hydroxide solution, and one 30 ml. portion of water. The procedure of Method 1 was then followed except that the final recrystallization was from ethanol.

N-(3-Tolyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine

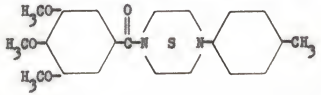


(a) Method 1

(b) Modifications -- 3,4,5-Trimethoxybenzoyl chloride (0.02 mole), N-(3-tolyl) piperazine (0.04 mole), and benzene (100 ml.)

were placed in a beaker and allowed to stand overnight. It was washed successively with two 30 ml. portions of 5% sodium hydroxide solution and one 30 ml. portion of water. The benzene was removed on a rotary evaporator; the residue was crystallized from 20 ml. of ethanol and treated by Method 1.

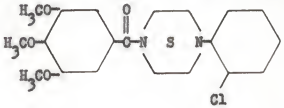
N-(4-Tolyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modifications -- The final recrystallization was from ether.

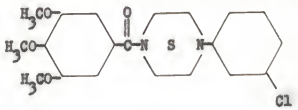
N-(2-Chlorophenyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modifications -- None

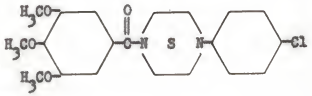
N-(3-Chlorophenyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modifications -- None

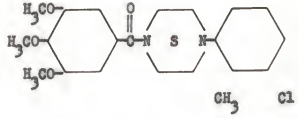
N-(4-Chlorophenyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modifications -- None

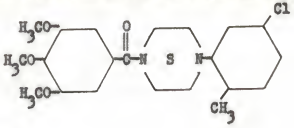
N-[(2-Methyl-3-chloro)phenyl]-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modifications -- The final recrystallisation was from a hexane-ethanol solution.

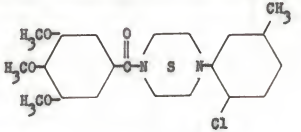
N-[(2-Methyl-5-chloro)phenyl]-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modifications -- None

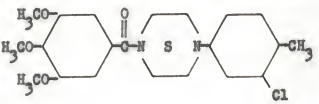
N-[(2-Chloro-5-methyl)phenyl]-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modifications -- None

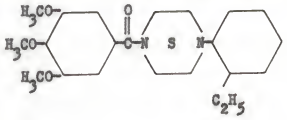
N-[(3-Chloro-4-methyl)phenyl]-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 1

(b) Modification -- The final recrystallization was from 50% aqueous ethanol.

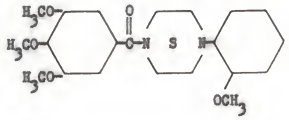
N-(2-Ethylphenyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 2

(b) Modifications -- None

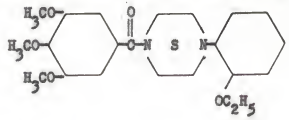
N-(2-Methoxyphenyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 2

(b) Modifications -- On evaporation of the chloroform, the residue was crystallized from 50 ml. of 50% aqueous ethanol.

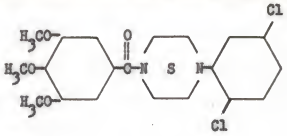
N-(2-Ethoxyphenyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 2

(b) Modifications -- None

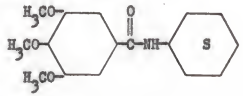
N-(2,5-Dichlorophenyl)-N'-(3,4,5-trimethoxybenzoyl)piperazine



(a) Method 2

(b) Modifications -- On evaporation of the chloroform, the residue crystallized. This was pulverized and washed with 50 ml. of ether. It was then recrystallized from ethanol.

N-Cyclohexyl-3,4,5-trimethoxybenzamide

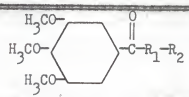


(a) Method 1

(b) Modifications -- The reagents were heated on the steam bath for ninety minutes. Then 200 ml. of chloroform was added and heating continued for thirty minutes. The mixture was then washed and evaporated as described in Method 1. The residue was crystallized and recrystallized from 200 ml. of ethanol.

TABLE I

PHYSICAL AND ANALYTICAL DATA OF 3,4,5-TRIMETHOXYBENZAMIDES



R_1	R_2	Molecular Formula	Molecular Weight
$-N(C_2H_4)_2N-$	CH_3-	$C_{15}H_{22}N_2O_4$	294.35
$-N(C_2H_4)_2N-$	$HOCH_2CH_2-$	$C_{16}H_{24}N_2O_5$	324.37
$-N(C_2H_4)_2N-$	C_6H_5-	$C_{20}H_{24}N_2O_4$	356.41
$-N(C_2H_4)_2N-$	$2-CH_3-C_6H_4-$	$C_{21}H_{26}N_2O_4$	370.44
$-N(C_2H_4)_2N-$	$3-CH_3-C_6H_4-$	$C_{21}H_{26}N_2O_4$	370.44
$-N(C_2H_4)_2N-$	$4-CH_3-C_6H_4-$	$C_{21}H_{26}N_2O_4$	370.44
$-N(C_2H_4)_2N-$	$2-Cl-C_6H_4-$	$C_{20}H_{23}ClN_2O_4$	390.86
$-N(C_2H_4)_2N-$	$3-Cl-C_6H_4-$	$C_{20}H_{23}ClN_2O_4$	390.86
$-N(C_2H_4)_2N-$	$4-Cl-C_6H_4-$	$C_{20}H_{23}ClN_2O_4$	390.86
$-N(C_2H_4)_2N-$	$2-CH_3-3-Cl-C_6H_3-$	$C_{21}H_{25}ClN_2O_4$	404.89
$-N(C_2H_4)_2N-$	$2-CH_3-5-Cl-C_6H_3-$	$C_{21}H_{25}ClN_2O_4$	404.89
$-N(C_2H_4)_2N-$	$2-Cl-5-CH_3-C_6H_3-$	$C_{21}H_{25}ClN_2O_4$	404.89

TABLE I (continued)

Melting Point	% Yield	Analyses %C Calcd. Found	%H Calcd. Found	%Cl Calcd. Found	%N Calcd. Found
118 -119.5	36	61.20 61.37	7.54 7.46	— —	9.52 9.38
82 - 84	40	59.24 59.34	7.46 7.41	— —	8.64 8.76
135.5-137	27	67.39 67.29	6.79 6.76	— —	7.86 7.44
132.5-133.5	27	68.08 68.32	7.08 7.03	— —	7.56 7.75
101.5-102	25	68.08 68.21	7.08 6.98	— —	7.56 7.25
108.5-109.5	32	68.08 68.33	7.08 7.17	— —	7.56 7.85
163.5-164.5	42	61.45 61.70	5.93 5.94	9.07 8.92	7.17 7.35
148 -149	35	61.45 61.82	5.93 5.74	9.07 9.25	7.17 6.95
137.5-139	34	61.45 61.73	5.93 5.68	9.07 8.94	7.17 6.86
135 -136	25	62.29 62.77	6.22 6.37	8.76 8.88	6.92 7.16
144 -146	32	62.29 62.70	6.22 6.08	8.76 8.66	6.92 7.06
169 -170.5	32	62.29 62.30	6.22 6.24	8.76 8.98	6.92 7.20

TABLE I (continued)

R_1	R_2	Molecular Formula	Molecular Weight
$-N(C_2H_4)_2N-$	$3-Cl-4-CH_3-C_6H_3-$	$C_{21}H_{25}ClN_2O_4$	404.89
$-N(C_2H_4)_2N-$	$2-C_2H_5-C_6H_4-$	$C_{22}H_{28}N_2O_4$	384.46
$-N(C_2H_4)_2N-$	$2-CH_3O-C_6H_4-$	$C_{21}H_{26}N_2O_5$	386.44
$-N(C_2H_4)_2N-$	$2-C_2H_5O-C_6H_4-$	$C_{22}H_{28}N_2O_5$	400.46
$-N(C_2H_4)_2N-$	$2,5-Cl_2-C_3H_6-$	$C_{20}H_{22}Cl_2N_2O_4$	425.31
$-NH-$	$C_6H_{11}-^*$	$C_{16}H_{23}NO_4$	293.35

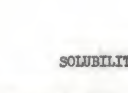
$C_6H_{11}-^*$ =

TABLE I (continued)

Melting Point	% Yield	Analyses %C Calcd. Found	%H Calcd. Found	%Cl Calcd. Found	%N Calcd. Found
124.5-125.5	37	62.29 62.68	6.22 6.22	8.76 9.01	6.92 6.84
101 -102	40	68.72 68.66	7.34 7.08	— —	7.29 7.31
114.5-116	53	65.26 65.10	6.78 6.68	— —	7.25 7.09
112 -113.5	40	65.98 66.24	7.05 6.99	— —	7.00 6.66
174 -176	60	56.48 56.32	5.21 5.25	16.67 16.90	6.58 6.18
182 -183	56	65.51 65.45	7.90 7.85	— —	4.78 4.44

TABLE II

SOLUBILITIES OF 3,4,5-TRIMETHOXYBENZAMIDES



S = Soluble
I = Insoluble
P = Partially Soluble

R_1	R_2	H_2O	5% HCl	5% NaOH	C_2H_5OH	$(C_2H_5)_2O$	C_6H_6
$-N(C_2H_4)_2N-$	CH_3-	S	S	S	S	S	S
$-N(C_2H_4)_2N-$	$HOCH_2CH_2-$	S	S	S	S	S	S
$-N(C_2H_4)_2N-$	C_6H_5-	I	I	I	S	I	S
$-N(C_2H_4)_2N-$	$2\text{-}CH_3\text{-}C_6H_4-$	I	I	I	S	I	S
$-N(C_2H_4)_2N-$	$3\text{-}CH_3\text{-}C_6H_4-$	I	I	I	S	I	S
$-N(C_2H_4)_2N-$	$4\text{-}CH_3\text{-}C_6H_4-$	I	I	I	S	I	S
$-N(C_2H_4)_2N-$	$2\text{-}Cl\text{-}C_6H_4-$	I	I	I	P	I	S
$-N(C_2H_4)_2N-$	$3\text{-}Cl\text{-}C_6H_4-$	I	I	I	P	I	S
$-N(C_2H_4)_2N-$	$4\text{-}Cl\text{-}C_6H_4-$	I	I	I	P	I	S
$-N(C_2H_4)_2N-$	$2\text{-}CH_3\text{-}3\text{-}Cl\text{-}C_6H_3-$	I	I	I	S	I	S
$-N(C_2H_4)_2N-$	$2\text{-}CH_3\text{-}5\text{-}Cl\text{-}C_6H_3-$	I	I	I	P	P	S
$-N(C_2H_4)_2N-$	$2\text{-}Cl\text{-}5\text{-}CH_3\text{-}C_6H_3-$	I	I	I	P	I	S
$-N(C_2H_4)_2N-$	$3\text{-}Cl\text{-}4\text{-}CH_3\text{-}C_6H_3-$	I	I	I	S	P	S
$-N(C_2H_4)_2N-$	$2\text{-}C_2H_5\text{-}C_6H_4-$	I	I	I	S	S	S
$-N(C_2H_4)_2N-$	$2\text{-}CH_3O\text{-}C_6H_4-$	I	I	I	S	S	S

TABLE II (continued)

S = Soluble
I = Insoluble
P = Partially Soluble

R_1	R_2	H_2O	5% HCl	5% NaOH	C_2H_5OH	$(C_2H_5)_2O$	C_6H_6
$-N(C_2H_4)_2N-$	$2-C_2H_5O-C_6H_4-$	I	I	I	S	S	S
$-N(C_2H_4)_2N-$	$2,5-Cl_2-C_6H_3-$	I	I	I	I	I	S
$-NH-$	$C_6H_{11}-$*	I	I	I	I	I	S

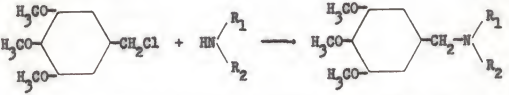
$C_6H_{11}-$* =

CHAPTER IV

3,4,5-TRIMETHOXYBENZYLAMINES

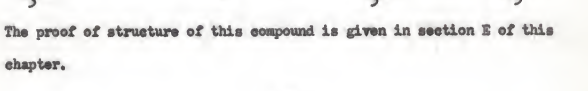
A. General

A group of twenty compounds was prepared by the reaction of 3,4,5-trimethoxybenzyl chloride with various amines (chiefly piperazines). All but one of these reactions led to the formation of 3,4,5-trimethoxybenzylamines.



Since compounds are easier to evaluate as drugs in water soluble form, the 3,4,5-trimethoxybenzylamines were converted to their hydrochloride derivatives; however, the free amines were also isolated and characterized.

The reaction of 3,4,5-trimethoxybenzyl chloride with N,N-dimethylhydrazine resulted in an almost quantitative yield of the hydrazinium chloride.



The proof of structure of this compound is given in section E of this chapter.

Instead of discussing the detailed preparation of each 3,4,5-trimethoxybenzylamine hydrochloride (and hydrazinium chloride), the author will report two general methods of preparation of these compounds. He will, therefore, state the general method used in its synthesis for each individual compound and will discuss any modifications of that method. The molecular formula, molecular weight, melting point, per cent yield and analytical data of each hydrochloride (and hydrazinium chloride) are tabulated on page 45 in Table III. The solubility data and the information as to whether each compound is a mono or dihydrochloride are reported in Table IV on page 49. It has been found that only the aliphatic nitrogens form hydrogen chloride salts under the conditions used in this investigation. The evidence for this will be presented in section E of this chapter.

Method 1 was used in preparing the earlier members of this series of hydrochlorides. Its chief disadvantage was that the products are somewhat soluble in acetone. In an attempt to avoid this difficulty, Method 2 was developed. It, however, had the disadvantage of slower kinetics. Both methods had the disadvantage of using aqueous hydrochloric acid. In the preparation of the compounds which formed dihydrochlorides (the N-alkyl piperazines) the precipitation of the product was difficult to accomplish if water was present.

If additional 3,4,5-trimethoxybenzylamine hydrochlorides are prepared, it is suggested that the following procedure be used.

Place 3,4,5-trimethoxybenzyl chloride (0.03 mole), N-substituted piperazine (0.06 mole) and acetone (100 ml.) in a flask and reflux for

six hours. Then remove the acetone on a rotary evaporator and add 200 ml. of ether. Filter the reaction mixture and reject the solids. Saturate the filtrate with hydrogen chloride gas and filter off the resulting product. Crystallize the product from water (or ethanol and benzene if it is a dihydrochloride) and recrystallize it from an ethanol–ether solution.

The pure 3,4,5-trimethoxybenzylamines were prepared in all cases from the appropriate hydrochloride by neutralizing the hydrochloride with 20% sodium hydroxide solution and adding acetone until the mixture was homogeneous. The solution was cooled in dry ice and water added until the solution became cloudy. The sides of the container were then scratched until the product started to crystallize. More water was then added and the free amine was filtered and dried. It was recrystallized from an ether–hexane solution. The molecular formula, molecular weight, melting point, per cent yield, and analytical data of each 3,4,5-trimethoxybenzylamine is tabulated in Table V on page 51. In all cases, these compounds are soluble in ethanol and acetone and insoluble in water.

It may be noted in Tables III and V that some compounds are reported on the basis of only a carbon–hydrogen analysis. This was done in the cases of the hydrochlorides in which a complete analysis (all elements except oxygen) had been made on the amine, and the hydrochloride was prepared from that sample of the amine.

The same is true of the amines for which only a carbon–hydrogen analysis is reported. (They were prepared from hydrochlorides on which a complete analysis had been made.)

The infrared spectra of all the compounds reported in this chapter were recorded on a Perkin-Elmer Infracord Spectrophotometer, Model 137B, using sodium chloride cells and prisms and are in the possession of Dr. H. H. Sisler of the University of Florida. Analyses of these spectra confirm the structures of the compounds.

B. Method 1

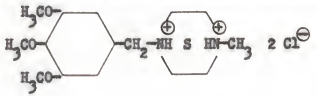
3,4,5-Trimethoxybenzyl chloride (0.04 mole), N-substituted piperazine (0.08 mole) and acetone (100 ml.) are placed in a flask and refluxed for four hours. The N-substituted piperazine hydrochloride which has precipitated is removed by filtration. Two ml. of 5% hydrochloric acid is then added to the filtrate to precipitate any remaining N-substituted piperazine. The mixture is again filtered and the filtrate made strongly acidic by the addition of 5 ml. of concentrated hydrochloric acid. The product now precipitates and is crystallized from water and recrystallized from an ether-ethanol solution.

C. Method 2

3,4,5-Trimethoxybenzyl chloride (0.03 mole), N-substituted piperazine (0.06 mole) and benzene (25 ml.) are placed in a beaker and allowed to stand twenty-four hours. The N-substituted piperazine hydrochloride which has precipitated is removed by filtration. These solids are washed with 25 ml. of ether and the filtrates combined. Five drops of concentrated hydrochloric acid are then added to the filtrates to precipitate any unreacted N-substituted piperazine and the mixture is again filtered. The filtrate is diluted with 100 ml. of ether and aqueous concentrated hydrochloric acid is added to the cloud point. The solid product which now precipitates is crystallized from water. The product is then converted to the free amine as described in section A of this chapter. This is recrystallized from a hexane-ether solution. The free amine is dissolved in ether and hydrogen chloride gas is used to saturate the solution. This reprecipitates the hydrochloride which is recrystallized from an ether-ethanol solution.

D. Individual Procedures

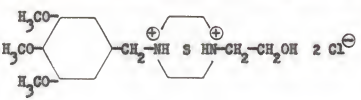
N-Methyl-N'-(3,4,5-trimethoxybenzyl)piperazine dihydrochloride



(a) Method 2

(b) Modifications -- 3,4,5-Trimethoxybenzyl chloride (0.04 mole), methylpiperazine (0.08 mole) and benzene (25 ml.) were used as starting materials. There was no precipitation on the addition of the five drops of concentrated hydrochloric acid or on the addition of the 5 ml. of that reagent. The solution was heated on the steam bath for fifteen minutes and the sides of the container scratched until the product crystallized. It was then recrystallized from a benzene-methanol solution. The dihydrochloride was converted to the free amine and the procedure of Method 2 followed from this point.

N-(2-Hydroxyethyl)-N'-(3,4,5-trimethoxybenzyl)piperazine dihydrochloride

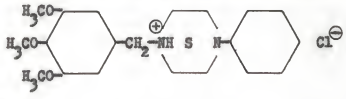


(a) Method 2

(b) Modifications -- On combining the ether washings of the

N-(2-hydroxyethyl)piperazine hydrochloride with the original filtrate, a precipitate formed. (This was found to be the free amine form of the product which is insoluble in ether.) Therefore, the solution was not diluted with ether. The combined filtrate was treated with 5 ml. of concentrated hydrochloric acid but no precipitate was formed. This solution was heated on the steam bath for fourteen hours. The mixture crystallized but also partially decomposed (the mixture turned black). The product was purified by recrystallizing it four times from methanol. This dihydrochloride was converted to the free amine which was recrystallized from an ether-benzene solution. The amine was reconverted to the dihydrochloride by dissolving the free amine in benzene and saturating the solution with hydrogen chloride gas. The dihydrochloride was then recrystallized from an ether-ethanol solution.

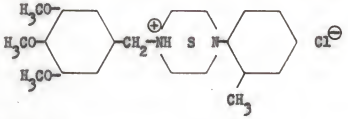
N-Phenyl-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 1

(b) Modifications -- After precipitating the unreacted N-phenylpiperazine as its hydrochloride, the solution was reduced in volume on the steam bath to 25 ml. and diluted with 100 ml. of ether. This solution was saturated with concentrated hydrochloric acid. The resulting precipitate was recrystallized from water and from an ether-ethanol solution.

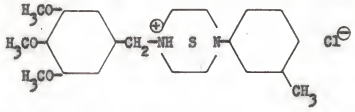
N-(2-Tolyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 1

(b) Modifications -- None

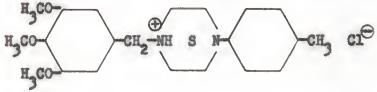
N-(3-Tolyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 1

(b) Modifications -- None

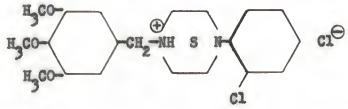
N-(4-Tolyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 1

(b) Modifications -- None

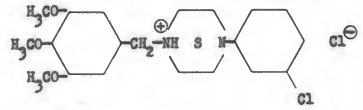
N-(2-Chlorophenyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 1

(b) Modifications -- After precipitating the unreacted N-(2-chlorophenyl)piperazine as the hydrochloride, the solution was reduced in volume on the steam bath to 25 ml. and diluted with 100 ml. of ether. Aqueous concentrated hydrochloride acid was added to the cloud point. The resulting precipitate was recrystallized from water and from an ether-ethanol solution.

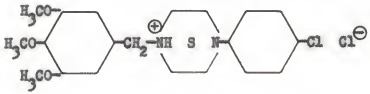
N-(3-Chlorophenyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 1

(b) Modifications -- None

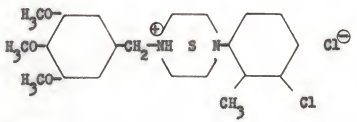
N-(4-Chlorophenyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 1

(b) Modifications -- None

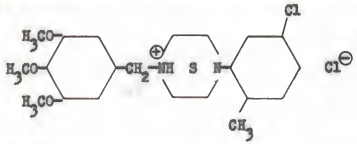
N-[(2-Methyl-5-chloro)phenyl]-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 1

(b) Modifications -- None

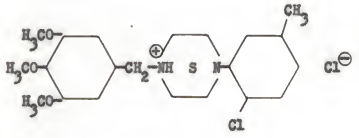
N-[(2-Methyl-5-chloro)phenyl]-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 1

(b) Modifications -- When the filtrate was made strongly acidic with 5 ml. of concentrated hydrochloric acid, no precipitation occurred. The acetone was then removed on a rotary evaporator and the residue washed into a beaker with water and a minimum volume of acetone. Five ml. of concentrated hydrochloric acid was then added to the solution. On cooling, precipitation occurred. The product was crystallized and recrystallized according to Method 1.

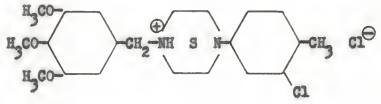
N-[(2-Chloro-5-methyl)phenyl]-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 2

(b) Modifications -- None

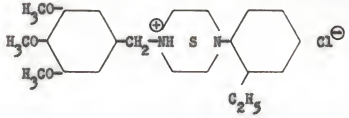
N-[(3-Chloro-4-methyl)phenyl]-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 2

(b) Modifications -- None

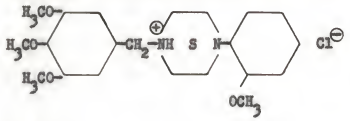
N-(2-Ethylphenyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 2

(b) Modifications -- None

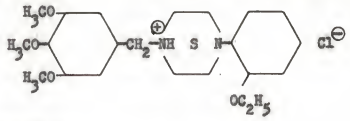
N-(2-Methoxyphenyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 2

(b) Modifications -- None

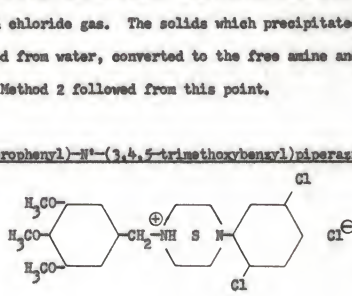
N-(2-Ethoxyphenyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 2

(b) Modifications -- After the reaction mixture was allowed to stand overnight and the solids removed by filtration, the filtrate was diluted with 150 ml. of ether. The solution was then saturated with hydrogen chloride gas. The solids which precipitated were recrystallized from water, converted to the free amine and the procedure of Method 2 followed from this point.

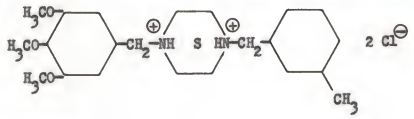
N-(2,5-Dichlorophenyl)-N'-(3,4,5-trimethoxybenzyl)piperazine hydrochloride



(a) Method 2

(b) Modifications -- None

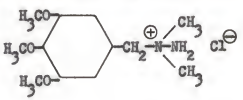
N-(3-Methylbenzyl)-N'-(3,4,5-trimethoxybenzyl)piperazine dihydrochloride



(a) Method 2

(b) Modifications -- None

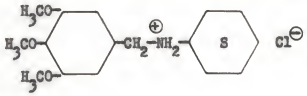
N,N-Dimethyl-N'-(3,4,5-trimethoxybenzyl)hydrazinium chloride



(a) Method 2

(b) Modifications -- When the reaction mixture was filtered after allowing it to stand overnight, a large amount of solids was obtained. This proved to be an almost quantitative yield (98%) of the hydrazinium chloride (see section E of this chapter). When this material was analysed without recrystallization, acceptable results were obtained.

N-Cyclohexyl-3,4,5-trimethoxybenzylamine hydrochloride



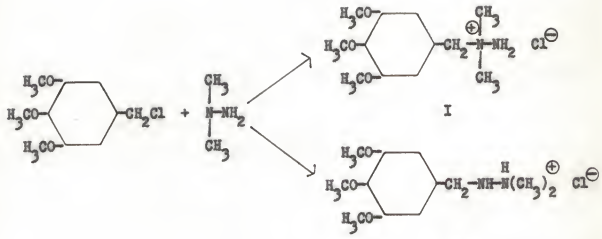
(a) Method 2

(b) Modifications -- When the 5 ml. of concentrated hydrochloric acid was added to the solution, no precipitation resulted. The solution was made basic with a sodium hydroxide solution and extracted with ether. The ether extract was distilled under vacuum. The N-cyclohexyl-3,4,5-trimethoxybenzylamine distilled at 162° (at 1.0 mm. Hg). The distillate was dissolved in ether and the solution saturated with hydrogen chloride gas. The precipitate was recrystallized twice from an ether-ethanol solution.

E. Proof of Structure

N,N-Dimethyl-N'-(3,4,5-trimethoxybenzyl)hydrazinium chloride

The question to be resolved was whether the reactants produced I or II.



I

II

Two grams of the compound were dissolved in 10 ml. of water and made basic to a pH of 11 with a 20% sodium hydroxide solution. This was extracted with three 15 ml. portions of ether. Hydrogen chloride was bubbled into the ether extract but no solids formed. The ether was evaporated, leaving a negligible residue (less than 0.01 g.). This is consistent with structure I but not II.

One gram of the compound was dissolved in water, shaken with silver oxide, and the resulting mixture filtered. A potentiometric titration was performed on the filtrate using 0.0956 N hydrochloric acid. The end point in the curve obtained by plotting pH vs ml. hydrochloric acid was almost as sharp as that obtained from the titration of a strong base with a strong acid. This is in agreement with the remarks of Sisler, et al.,[17] on the basic strength of hydrazinium hydroxides. This evidence is again consistent with I but not II.

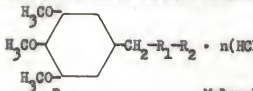
Reasons for assignment of hydrochloride structures

Only in three cases were dihydrochlorides obtained in the 3,4,5-trimethoxybenzylamine series. In no case did an amine having nitrogen attached to an aryl group atom form a dihydrochloride. The three cases of dihydrochlorides occurred with amines having two aliphatic nitrogen atoms. (This might be expected from the well known difference in basicity of alkyl and aryl amines.) It is for these reasons that the author has assumed that the proton from the hydrogen chloride is attached to the nitrogen atom to which no aryl groups are attached.

TABLE III

PHYSICAL AND ANALYTICAL DATA OF

3,4,5-TRIMETHOXYBENZYLAMINE HYDROCHLORIDES



R_1	R_2	Molecular Formula	Molecular Weight
$-N(C_2H_4)_2N-$	CH_3-	$C_{15}H_{26}Cl_2N_2O_3$	353.29
$-N(C_2H_4)_2N-$	HOC_2H_4-	$C_{16}H_{28}Cl_2N_2O_4$	383.31
$-N(C_2H_4)_2N-$	C_6H_4-	$C_{20}H_{27}ClN_2O_3$	378.90
$-N(C_2H_4)_2N-$	$2-CH_3-C_6H_4-$	$C_{21}H_{29}ClN_2O_3$	392.92
$-N(C_2H_4)_2N-$	$3-CH_3-C_6H_4-$	$C_{21}H_{29}ClN_2O_3$	392.92
$-N(C_2H_4)_2N-$	$4-CH_3-C_6H_4-$	$C_{21}H_{29}ClN_2O_3$	392.92
$-N(C_2H_4)_2N-$	$2-Cl-C_6H_4-$	$C_{20}H_{26}Cl_2N_2O_3$	413.34
$-N(C_2H_4)_2N-$	$3-Cl-C_6H_4-$	$C_{20}H_{26}Cl_2N_2O_3$	413.34
$-N(C_2H_4)_2N-$	$4-Cl-C_6H_4-$	$C_{20}H_{26}Cl_2N_2O_3$	413.34
$-N(C_2H_4)_2N-$	$2-CH_3-3-Cl-C_6H_3-$	$C_{21}H_{28}Cl_2N_2O_3$	427.36
$-N(C_2H_4)_2N-$	$2-CH_3-5-Cl-C_6H_3-$	$C_{21}H_{28}Cl_2N_2O_3$	427.36
$-N(C_2H_4)_2N-$	$2-Cl-5-CH_3-C_6H_3-$	$C_{21}H_{28}Cl_2N_2O_3$	427.36

TABLE III (continued)

D = Melts with Decomposition

Melting Point		% Yield	Analyses %C Calcd. Found	%H Calcd. Found	%Cl Calcd. Found	%N Calcd. Found
237–238	D	53	50.99 51.15	7.42 7.48	20.07 19.72	— —
226–227	D	30	50.13 50.52	7.36 7.33	18.50 18.65	— —
263–264	D	70	63.39 63.25	7.18 7.32	9.36 9.28	7.40 7.24
210–212	D	40	64.19 64.17	7.44 7.41	9.02 9.04	7.13 7.07
262–263	D	33	64.19 64.04	7.44 7.35	9.02 9.35	7.13 7.06
263–264	D	36	64.19 64.15	7.44 7.51	9.02 9.17	7.13 7.25
230–231	D	47	58.11 58.40	6.34 6.63	17.16 16.95	6.78 6.83
244–245.5	D	53	58.11 58.19	6.34 6.26	17.16 17.04	6.78 7.05
246–247	D	51	58.11 57.81	6.34 6.25	17.16 16.75	6.78 6.81
219–220	D	33	59.02 58.85	6.60 6.91	16.59 16.23	6.56 6.55
209–210	D	36	59.02 59.02	6.60 6.57	16.59 16.85	6.56 6.50
228–229	D	48	59.02 59.16	6.60 6.62	— —	— —

TABLE III (continued)

R_1	R_2	Molecular Formula	Molecular Weight
$-N(C_2H_4)_2N-$	$3-Cl-4-CH_3-C_6H_3-$	$C_{21}H_{28}Cl_2N_2O_3$	427.36
$-N(C_2H_4)_2N-$	$2-C_2H_5-C_6H_4-$	$C_{22}H_{31}ClN_2O_3$	406.95
$-N(C_2H_4)_2N-$	$2-CH_3O-C_6H_4-$	$C_{21}H_{29}ClN_2O_4$	408.92
$-N(C_2H_4)_2N-$	$2-C_2H_5O-C_6H_4-$	$C_{22}H_{31}ClN_2O_4$	422.95
$-N(C_2H_4)_2N-$	$2,5-Cl_2-C_6H_3-$	$C_{20}H_{25}Cl_3N_2O_3$	447.79
$-N(C_2H_4)_2N-$	$3-CH_3-C_6H_4-CH_2-$	$C_{22}H_{32}Cl_2N_2O_3$	443.41
$-(CH_3)_2\overset{+}{N}-^{*}\ Cl^-$	NH_2-	$C_{12}H_{21}ClN_2O_3$	276.77
$-NH-$	$C_6H_{11}-^{**}$	$C_{16}H_{26}ClNO_3$	315.84

$-(CH_3)_2N-^{*}$ – Note that this compound is a hydrazinium chloride rather than an amine hydrochloride.

$C_6H_{11}-^{**}$ =

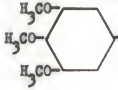
TABLE III (continued)

D = Melts with Decomposition

Melting Point		% Yield	Analyses			
			%C Calcd. Found	%H Calcd. Found	%Cl Calcd. Found	%N Calcd. Found
247–248	D	43	59.02 58.79	6.60 6.58	— —	— —
198–199	D	40	64.93 65.05	7.68 7.52	— —	— —
222–223	D	42	61.68 61.77	7.15 6.89	— —	— —
216–217	D	36	62.47 62.28	7.39 7.17	— —	— —
211–212	D	54	53.64 54.04	5.63 5.85	— —	— —
234–235	D	55	59.59 59.78	7.28 7.22	15.99 16.23	— —
183–184		98	52.09 51.96	7.65 7.51	12.82 13.10	10.13 10.48
150–151		20	60.84 61.21	8.30 8.16	11.23 11.50	4.44 4.23

TABLE IV

SOLUBILITIES OF 3,4,5-TRIMETHOXYBENZYLAMINE HYDROCHLORIDES



S = Soluble
I = Insoluble
P = Partially Soluble
R = Reacts with Solvent

R_1	R_2	H_2O	5% HCl	5% NaOH	C_2H_5OH	$(C_2H_5)_2O$	C_6H_6	n
$-N(CH_2CH_2)_2N-$	CH_3-	S	S	R	S	I	P	2
$-N(CH_2CH_2)_2N-$	HOC_2H_4-	S	S	R	I	I	I	2
$-N(CH_2CH_2)_2N-$	C_6H_5-	I	I	R	P	I	P	1
$-N(CH_2CH_2)_2N-$	$2\text{-}CH_3\text{-}C_6H_4-$	I	I	R	S	I	P	1
$-N(CH_2CH_2)_2N-$	$3\text{-}CH_3\text{-}C_6H_4-$	I	I	R	P	I	P	1
$-N(CH_2CH_2)_2N-$	$4\text{-}CH_3\text{-}C_6H_4-$	I	I	R	P	I	P	1
$-N(CH_2CH_2)_2N-$	$2\text{-}Cl\text{-}C_6H_4-$	I	I	R	P	I	P	1
$-N(CH_2CH_2)_2N-$	$3\text{-}Cl\text{-}C_6H_4-$	I	I	R	P	I	P	1
$-N(CH_2CH_2)_2N-$	$4\text{-}Cl\text{-}C_6H_4-$	I	I	R	S	I	P	1
$-N(CH_2CH_2)_2N-$	$2\text{-}CH_3\text{-}3\text{-}Cl\text{-}C_6H_3-$	I	I	R	S	I	P	1
$-N(CH_2CH_2)_2N-$	$2\text{-}CH_3\text{-}5\text{-}Cl\text{-}C_6H_3-$	I	I	R	S	I	I	1
$-N(CH_2CH_2)_2N-$	$2\text{-}Cl\text{-}5\text{-}CH_3\text{-}C_6H_3-$	I	I	R	P	I	P	1
$-N(CH_2CH_2)_2N-$	$3\text{-}Cl\text{-}4\text{-}CH_3\text{-}C_6H_3-$	I	I	R	P	I	P	1
$-N(CH_2CH_2)_2N-$	$2\text{-}C_2H_5\text{-}C_6H_4-$	I	I	R	S	I	P	1

TABLE IV (continued)

S = Soluble
I = Insoluble
P = Partially Soluble
R = Reacts with Solvent

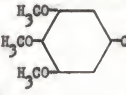
R_1	R_2	H_2O	5% HCl	5% NaOH	C_2H_5OH	$(C_2H_5)_2O$	C_6H_6	n
$-N(CH_2CH_2)_2N-$	$2\text{-}CH_3O\text{-}C_6H_4-$	S	S	R	S	I	S	1
$-N(CH_2CH_2)_2N-$	$2\text{-}C_2H_5O\text{-}C_6H_4-$	S	S	R	S	I	I	1
$-N(CH_2CH_2)_2N-$	$2,5\text{-}Cl_2\text{-}C_6H_3-$	I	I	R	S	I	P	1
$-N(CH_2CH_2)_2N-$	$3\text{-}CH_3\text{-}C_6H_4\text{-}CH_2-$	S	S	R	S	I	I	2
$-(CH_3)_2\overset{\oplus}{N}\text{-}\,Cl^{\ominus}$ *	NH_2-	S	S	R	S	I	I	0
$-NH-$	$-C_6H_{11}$ **	S	S	R	S	I	S	1

$(CH_3)_2N-$* – Note that this compound is a hydrazinium chloride rather than an amine hydrochloride.

$C_6H_{11}-$** –

TABLE V

PHYSICAL AND ANALYTICAL DATA OF 3,4,5-TRIMETHOXYBENZYLAMINES



R_1	R_2	Molecular Formula	Molecular Weight
$-N(C_2H_4)_2N-$	CH_3-	$C_{15}H_{24}N_2O_3$	280.36
$-N(C_2H_4)_2N-$	HOC_2H_4-	$C_{16}H_{26}N_2O_4$	310.39
$-N(C_2H_4)_2N-$	C_6H_5-	$C_{20}H_{26}N_2O_3$	342.43
$-N(C_2H_4)_2N-$	$2-CH_3-C_6H_4-$	$C_{21}H_{28}N_2O_3$	356.45
$-N(C_2H_4)_2N-$	$3-CH_3-C_6H_4-$	$C_{21}H_{28}N_2O_3$	356.45
$-N(C_2H_4)_2N-$	$4-CH_3-C_6H_4-$	$C_{21}H_{28}N_2O_3$	356.45
$-N(C_2H_4)_2N-$	$2-Cl-C_6H_4-$	$C_{20}H_{25}ClN_2O_3$	376.88
$-N(C_2H_4)_2N-$	$3-Cl-C_6H_4-$	$C_{20}H_{25}ClN_2O_3$	376.88
$-N(C_2H_4)_2N-$	$4-Cl-C_6H_4-$	$C_{20}H_{25}ClN_2O_3$	376.88
$-N(C_2H_4)_2N-$	$2-CH_3-3-Cl-C_6H_3-$	$C_{21}H_{27}ClN_2O_3$	390.91
$-N(C_2H_4)_2N-$	$2-CH_3-5-Cl-C_6H_3-$	$C_{21}H_{27}ClN_2O_3$	390.91
$-N(C_2H_4)_2N-$	$2-Cl-5-CH_3-C_6H_3-$	$C_{21}H_{27}ClN_2O_3$	390.91

TABLE V (continued)

Melting Point	Analyses			
	%C Calcd. Found	%H Calcd. Found	%Cl Calcd. Found	%N Calcd. Found
88 - 89	64.26 64.37	8.63 8.81	— —	9.99 10.18
83.5- 84.5	61.91 62.00	8.44 8.51	— —	9.03 9.30
80 - 81	70.15 70.16	7.65 7.47	— —	— —
90.5- 91.5	70.76 70.83	7.92 7.96	— —	7.86 7.75
56.5- 57.5	70.76 70.80	7.92 7.81	— —	— —
98.5- 99.5	70.76 70.49	7.92 7.62	— —	— —
107 -108	63.73 63.55	6.69 6.68	9.41 9.65	7.43 7.17
86 - 87	63.73 63.51	6.69 6.68	9.41 9.53	7.43 7.05
70 - 71	63.73 63.58	6.69 6.69	9.41 9.15	7.43 7.15
96 - 97	64.52 64.33	6.96 6.85	— —	— —
84 - 85	64.52 64.28	6.96 6.90	9.07 9.31	7.17 7.21
64 - 65	64.52 64.40	6.96 6.72	9.07 9.05	7.17 7.40

TABLE V (continued)

R_1	R_2	Molecular Formula	Molecular Weight
$-N(C_2H_4)_2N-$	$3-Cl-4-CH_3-C_6H_3-$	$C_{21}H_{27}ClN_2O_3$	390.91
$-N(C_2H_4)_2N-$	$2-C_2H_5-C_6H_4-$	$C_{22}H_{30}N_2O_3$	370.48
$-N(C_2H_4)_2N-$	$2-CH_3O-C_6H_4-$	$C_{21}H_{28}N_2O_4$	372.45
$-N(C_2H_4)_2N-$	$2-C_2H_5O-C_6H_4-$	$C_{22}H_{30}N_2O_4$	386.48
$-N(C_2H_4)_2N-$	$2,5-Cl_2-C_6H_3-$	$C_{20}H_{24}Cl_2N_2O_3$	411.32
$-N(C_2H_4)_2N-$	$3-CH_3-C_6H_4-CH_2-$	$C_{22}H_{30}N_2O_3$	370.48
$-NH-$	$C_6H_{11}-^*$	$C_{16}H_{25}NO_3$	279.37

$C_6H_{11}-^*$ =

TABLE V (continued)

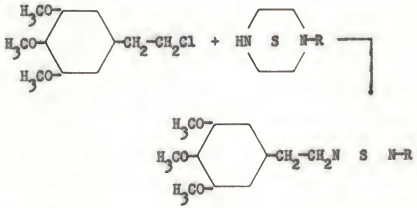
Melting Point	Analyses %C Calcd. Found	%H Calcd. Found	%Cl Calcd. Found	%N Calcd. Found
76.5- 77.5	64.52 64.66	6.96 6.90	9.07 9.21	7.17 7.24
75 - 76	71.32 71.25	8.16 8.03	— —	7.56 7.59
69 - 70	67.72 67.75	7.58 7.82	— —	7.52 7.86
103.5-104.5	68.37 68.43	7.82 7.75	— —	7.25 7.32
85 - 86	58.40 58.40	5.88 5.88	6.81 7.09	17.24 17.12
89.5- 90.5	71.32 71.01	8.16 8.05	— —	7.56 7.81
b.p. 162°/1 mm. Hg	68.78 68.74	9.02 9.11	— —	5.01 4.76

CHAPTER V

2-(3,4,5-TRIMETHOXYPHENYL)ETHYLPIPERAZINES

A. General

A group of eight compounds was prepared by the reaction of 2-(3,4,5-trimethoxyphenyl)ethyl chloride with various N-substituted piperazines.



Because of the relative difficulty of preparation of this substituted ethyl chloride, only the amine compounds whose 2-(3,4,5-trimethoxyphenyl)ethyl derivatives would have the greatest chance of being beneficial drugs were reacted with it.

In a private conversation with Dr. R. F. Parcell of Parke, Davis and Company, it was decided that the greatest possibility of obtaining compounds having beneficial physiological activity would be from the syntheses of the 2-(3,4,5-trimethoxyphenyl)ethyl derivatives of the piperazines having the following substituents: N-methyl, N-phenyl, N-(3-tolyl), N-(2-chlorophenyl),

N-(2-methyl-5-chloro)phenyl, N-(2-chloro-5-methyl)phenyl, N-(2,5-dichlorophenyl) and N-(2-ethoxyphenyl).

Because compounds are easier to evaluate as drugs in water soluble form, the N-substituted-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]-piperazines were converted to their hydrochloride derivatives.

Rather than discuss in detail the preparation of each compound, the author will state in detail the standard procedure used in preparing these compounds. He will report any modifications in that method for each compound. The molecular formula, molecular weight, melting point, per cent yield and analytical data of each N-substituted-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine hydrochloride are recorded in Table VI on page 64. The solubility data and information as to whether the compound is a mono or dihydrochloride are in Table VII on page 66. In all cases only the aliphatic nitrogen atoms are considered to be sufficiently basic (under the experimental conditions) to form hydrochlorides. The evidence for this is stated in section E of Chapter IV.

Attempts were made to isolate the N-substituted-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazines which resulted in partial success. The procedures used and the results obtained are discussed in section D of this chapter.

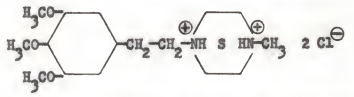
The infrared spectra of all the compounds reported in this chapter were recorded on a Perkin-Elmer Infracord Spectrophotometer, Model 137B, using sodium chloride cells and prisms and are in the possession of Dr. H. H. Sisler of the University of Florida. Analyses of these spectra confirm the structures of the compounds.

B. Standard Method

2-(3,4,5-Trimethoxyphenyl)ethyl chloride (0.04 mole), N-substituted piperazine (0.04 mole), sodium carbonate (0.04 mole) and 50% aqueous ethanol (200 ml.) are placed in a flask and refluxed for one week. The volume of the reaction mixture is reduced to 75 ml. on a rotary evaporator and extracted three times with 150 ml. portions of ether. The ether extracts are then combined and reduced to a volume of 300 ml. on a steam bath. This solution is now saturated with hydrogen chloride gas. The precipitate is dissolved in ethanol and enough ether added to the solution to reprecipitate the hydrochloride. Finally, the hydrochloride is recrystallized from water.

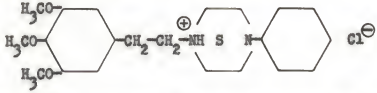
C. Individual Procedures

N-Methyl-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine dihydrochloride



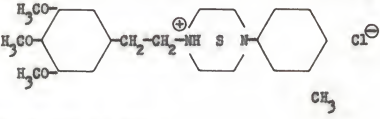
Modifications -- After the product was precipitated (on saturating the ether solution with hydrogen chloride gas), it was crystallized twice from a 2% aqueous ethanol solution.

N-Phenyl-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine hydrochloride



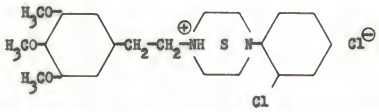
Modifications -- After the reaction mixture had been extracted three times with 150 ml. portions of ether, the extracts were combined and reduced to 100 ml. on a steam bath. To this solution, 100 ml. of water and 25 ml. of acetone were added and the mixture heated on the steam bath until all the ether had evaporated. At this point the free piperazine was in the form of an insoluble viscous liquid. The mixture was cooled in dry ice and when the viscous liquid was scratched against the walls of the container, the viscous liquid solidified. This solid was dried by filtration and a small portion reserved for identification studies (see section D of this chapter). The remainder of the solid was dissolved in 300 ml. of ether and solution saturated with hydrogen chloride gas. The product which precipitated was treated according to the standard procedure.

N-(3-Tolyl)-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine hydrochloride



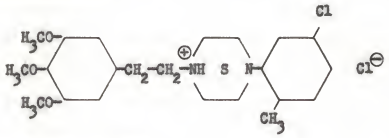
Modifications -- None

N-(2-Chlorophenyl)-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine hydrochloride



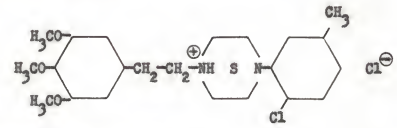
Modifications -- The product was purified by crystallization from water and recrystallization from ethanol.

N-[(2-Methyl-5-chloro)phenyl]-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]-piperazine hydrochloride



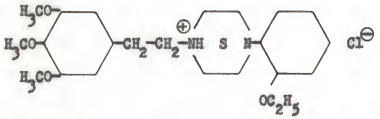
Modifications -- None

N-[(2-Chloro-5-methyl)phenyl]-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]-piperazine hydrochloride



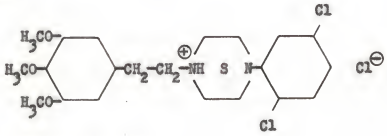
Modifications -- None

N-(2-Ethoxyphenyl)-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine hydrochloride



Modifications -- None

N-(2,5-Dichlorophenyl)-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine hydrochloride



Modifications -- None

D. Attempted Isolation of the Free Piperazines

As was stated earlier in this chapter, the attempt to isolate the N-substituted-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazines in their free amine form met with only partial success. In all cases a small amount (about 0.1 g.) of the appropriate hydrochloride was neutralized with 20% sodium hydroxide solution and acetone added

until the mixture was homogeneous. The solution was cooled in a dry ice bath and water was added until the solution became cloudy. It was then cooled and the walls of the container scratched vigorously to induce crystallization. If crystallization did not occur within fifteen minutes, the scratching and cooling were discontinued and the mixture was allowed to stand for one week. The results obtained from each of the N-substituted-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]-piperazine hydrochlorides are reported in the following paragraphs.

N-Methyl-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine

This free amine was soluble in the basic aqueous acetone solution. The acetone was evaporated on a steam bath but the amine remained in solution. The solution was extracted with ether and the ether layer evaporated to dryness at room temperature. An oily residue remained, which is probably the stable form of this compound at room temperature.

N-Phenyl-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine

On cooling and scratching the walls of the container, crystallization occurred. This solid had the same melting point as the unknown solid that was synthesized in the preparation of the N-phenyl-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine hydrochloride. A "mixed melting point" determination of these solids showed no lowering of the melting point. Although this solid melted at 68-70°, the liquid remained opaque until the temperature reached

100° at which point the solution boiled slightly and became transparent. When a weighed sample of the solid was dried overnight at 40° in a vacuum oven, the solid melted. The sample's loss of weight was determined. If one assumes the solid to be the monohydrate of the free amine, it should contain 4.82% of water. The loss in weight of the sample was 4.91%. Infrared spectra of the solid and liquid were identical except for a peak at 3400 cm.$^{-1}$ which is in the correct position for an OH peak.[18] The evidence is all mutually consistent if we consider the solid to be the monohydrate of a liquid, free amine.

N-(3-Tolyl)-N'-2-[(3,4,5-trimethoxyphenyl)ethyl]piperazine

On cooling, and scratching the walls of the container, crystallization occurred. The solid melted at 91-92°. Its infrared spectrum did not show a peak in the OH region.[18]

N-(2-Chlorophenyl)-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine; N-[(2-chloro-5-methyl)phenyl]-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]-piperazine; and N-(2-ethoxyphenyl)-N'-[2-(3,4,5-trimethoxyphenyl)-ethyl]piperazine

These compounds were treated by the general procedure described previously but did not crystallize. The free amines were in the form of viscous liquids. Although the free amines could probably have been crystallized if sufficient time and effort had been devoted to the attempt, the aims of this investigation did not require this operation.

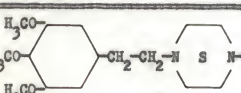
N-[(2-Methyl-5-chloro)phenyl]-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]-piperazine and N-(2,5-dichlorophenyl)-N'-[2-(3,4,5-trimethoxyphenyl)-ethyl]piperazine

These compounds crystallized when they were allowed to stand for one week. The N-(2-methyl-5-chloro)phenyl-N'-[2-(3,4,5-trimethoxy-phenyl)ethyl]piperazine had a melting point of 119-121°. The N-(2,5-dichlorophenyl)-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine melted at 99.5-101.5°. Their infrared spectra did not show peaks in the OH region.[18]

TABLE VI

PHYSICAL AND ANALYTICAL DATA OF

2-(3,4,5-TRIMETHOXYPHENYL)ETHYLPIPERAZINE HYDROCHLORIDES



D = Melts with Decomposition

R	Molecular Formula	Molecular Weight	Melting Point	
CH_3-	$C_{16}H_{28}Cl_2N_2O_3$	367.31	271-272	D
C_6H_5-	$C_{21}H_{29}ClN_2O_3$	392.92	242-243	D
3-CH_3-C_6H_4-	$C_{22}H_{31}ClN_2O_3$	406.95	251-252	D
2-Cl-C_6H_4-	$C_{21}H_{28}Cl_2N_2O_3$	427.36	242-243	D
2-CH_3-5-Cl-C_6H_3-	$C_{22}H_{30}Cl_2N_2O_3$	441.39	232-233	D
2-Cl-5-CH_3-C_6H_3-	$C_{22}H_{30}Cl_2N_2O_3$	441.39	237-238	D
2-C_2H_5O-C_6H_4-	$C_{23}H_{33}ClN_2O_4$	436.97	208-209	D
2,5-Cl_2-C_6H_3-	$C_{21}H_{27}Cl_3N_2O_3$	461.82	227-228	D

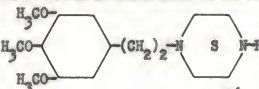
TABLE VI (continued)

% Yield	Analyses %C Calcd. Found	%H Calcd. Found	%Cl Calcd. Found	%N Calcd. Found
27	52.32 52.22	7.68 7.45	19.31 19.34	7.63 7.44
33	64.19 64.04	7.44 7.21	9.02 8.92	7.13 7.24
25	64.93 65.00	7.68 7.44	8.71 8.43	6.89 7.02
39	59.02 59.16	6.60 6.42	16.59 16.68	6.56 6.36
43	59.86 59.43	6.85 6.78	16.07 16.40	6.35 6.65
51	59.86 60.02	6.85 6.82	16.07 16.35	6.35 6.21
40	63.21 63.56	7.61 7.50	8.11 8.26	6.41 6.56
39	54.61 54.52	5.89 6.08	23.03 23.22	6.07 5.86

TABLE VII

SOLUBILITIES OF

2-(3,4,5-TRIMETHOXYPHENYL)ETHYLPIPERAZINE HYDROCHLORIDES



S = Soluble
I = Insoluble
P = Partially Soluble
R = Reacts with Solvent

R	H_2O	5% HCl	5% NaOH	C_2H_5OH	$(C_2H_5)_2O$	C_6H_6	n
CH_3-	S	S	R	I	I	P	2
C_6H_5-	I	I	R	S	I	I	1
3-CH_3-C_6H_4-	I	I	R	P	I	P	1
2-Cl-C_6H_4-	I	I	R	S	I	P	1
2-CH_3-5-Cl-C_6H_3-	I	I	R	S	I	S	1
2-Cl-5-CH_3-C_6H_3-	I	I	R	P	I	P	1
2-C_2H_5O-C_6H_4-	I	I	R	P	I	I	1
2,5-Cl_2-C_6H_3-	I	I	R	I	P	I	1

CHAPTER VI

SUMMARY

The 3,4,5-trimethoxybenzoyl; 3,4,5-trimethoxybenzyl; and 2-(3,4,5-trimethoxyphenyl)ethyl derivatives of a number of amines (chiefly N-substituted piperazines) were prepared and a study was made of their modes of formation. Forty-six new compounds, which are to be evaluated as drugs, were synthesized and characterized during this study. Specific structures have been assigned to each of these new compounds. These structures were based on both chemical and physical evidence. In addition, an improved synthesis of 3,4,5-trimethoxybenzyl cyanide was developed in the course of this investigation.

A general procedure was developed for the preparation of the 3,4,5-trimethoxybenzamides by the reaction of 3,4,5-trimethoxybenzoyl chloride with amines. Eighteen of these compounds were prepared. In seventeen of these compounds, the amine from which the 3,4,5-trimethoxybenzamide was formed was an N-substituted piperazine. These N-substituents are methyl; 2-hydroxyethyl; phenyl; 2-tolyl; 3-tolyl; 4-tolyl; 2-chlorophenyl; 3-chlorophenyl; 4-chlorophenyl; (2-methyl-3-chloro)phenyl; (2-methyl-5-chloro)phenyl; (2-chloro-5-methyl)phenyl; (3-chloro-4-methyl)phenyl; 2-ethylphenyl; 2-methoxyphenyl; 2-ethoxyphenyl; and 2,5-dichlorophenyl. The other amine used was cyclohexyl amine.

The infrared spectra of these amides show carbonyl absorption of energy in the range 1610-1640 cm.$^{-1}$. This corresponds to a rather low energy for carbonyl absorption; however, one might expect this because of the electronic release of the 3,4,5-trimethoxyphenyl group which would be expected to lower the amount of double bond character in the carbonyl group.

A general method was also developed for the synthesis of 3,4,5-trimethoxybenzylamine hydrochlorides by the reaction of 3,4,5-trimethoxybenzyl chloride with amines. Nineteen 3,4,5-trimethoxybenzylamine hydrochlorides are reported. Eighteen of them were synthesized from N-substituted piperazines. These N-substituents are methyl; 2-hydroxyethyl; phenyl; 2-tolyl; 3-tolyl; 4-tolyl; 2-chlorophenyl; 3-chlorophenyl; 4-chlorophenyl; (2-methyl-3-chloro)-phenyl; (2-methyl-5-chloro)phenyl; (2-chloro-5-methyl)phenyl; (3-chloro-4-methyl)phenyl; 2-ethylphenyl; 2-methoxyphenyl; 2-ethoxyphenyl; 2,5-dichlorophenyl; and 3-methylbenzyl. The preparation of N-cyclohexyl-3,4,5-trimethoxybenzylamine hydrochloride is also reported. The nineteen preceding compounds were characterized both as hydrochlorides and as free amines. One additional compound, N,N-dimethyl-N'-(3,4,5-trimethoxybenzyl)hydrazinium chloride, was synthesized by the same general method as the preceding nineteen compounds.

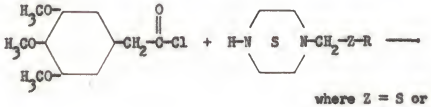
The N-alkyl-N'-(3,4,5-trimethoxybenzyl)piperazines form dihydrochlorides under the experimental conditions, whereas the N-aryl-N'-(3,4,5-trimethoxybenzyl)piperazines form monohydrochlorides. These dihydrochlorides are very soluble in water; however, the

monohydrochlorides are only slightly soluble in water. In general, the solubilities of the monohydrochlorides are about 4 g. per 100 ml. of boiling water and less than 1 g. per 100 ml. of water at room temperature. It would require additional studies to determine if the great difference in solubilities of the mono and dihydrochlorides is because of the presence of the aryl group or is an effect of the number of protonated nitrogen atoms in the molecule. This question could be resolved by preparing a few N-aryl-N'-(3,4,5-trimethoxybenzyl)-piperazine dihydrochlorides and several N-alkyl-N'-(3,4,5-trimethoxybenzyl)piperazine monohydrochlorides and determining the solubilities of these compounds.

Eight new N-substituted-N'-2-(3,4,5-trimethoxyphenyl)ethyl piperazine hydrochlorides were prepared by a general procedure which involved the reaction of 2-(3,4,5-trimethoxyphenyl)ethyl chloride with N-substituted piperazines. These N-substituents are methyl; phenyl; 3-tolyl; 2-chlorophenyl; (2-methyl-5-chloro)phenyl; (2-chloro-5-methyl)phenyl; 2-ethoxyphenyl; and 2,5-dichlorophenyl. The hydrochlorides of the N-methyl-N'-[2-(3,4,5-trimethoxyphenyl)ethyl]piperazine dihydrochloride and the N-aryl-N'-2[(3,4,5-trimethoxyphenyl)ethyl]-piperazine monohydrochlorides exhibit the same differences in water solubility as did the N-alkyl and N-aryl-N'-2[(3,4,5-trimethoxybenzyl)-piperazine] hydrochlorides.

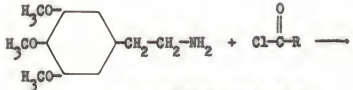
A synthesis of 3,4,5-trimethoxybenzyl cyanide, far superior to any synthesis found in the literature, was also developed. It involved the reaction of 3,4,5-trimethoxybenzyl chloride with sodium cyanide under S_N2 conditions. This affords an excellent method of

preparing compounds for which 3,4,5-trimethoxybenzyl cyanide is an intermediate, such as 3,4,5-trimethoxyphenylacetyl chloride; 3,4,5-trimethoxyphenylacetamide; mescaline; and 2-(3,4,5-trimethoxyphenyl)-ethyl chloride. The availability of these compounds would enable one to continue the study of the 2-(3,4,5-trimethoxyphenyl)ethyl compounds in various ways. A few of the reactions which suggest themselves are

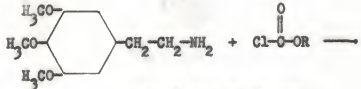


where Z = S or O

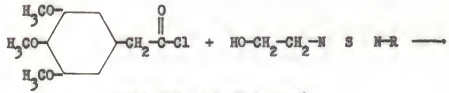
R = alkyl or aryl



where R = alkyl or aryl



where R = alkyl or aryl



where R = alkyl or aryl

The results of the physiological evaluation of these compounds would also help in determining the direction in which this investigation could be extended.

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BIOGRAPHICAL ITEMS

Bernard Silverman was born in Philadelphia, Pennsylvania, on November 1, 1932, and attended elementary school in that city. He attended secondary school in Jacksonville, Florida, and graduated from Robert E. Lee High School in June, 1950. In September, 1950, he entered the University of Florida and in June, 1954, received the degree of Bachelor of Science in Chemistry with high honors.

During the period of March, 1955, to June, 1957, he served as an officer in the United States Air Force. He re-entered the University of Florida in June, 1957, and commenced working toward the Ph.D. degree with a Major in Organic Chemistry.

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This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of that committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council, and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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